

Declaration of Janice M. Troha
App. Serial No. 10/788,277



PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:

) Group Art Unit: 1614

ROSENTHAL et al.

) Examiner: Roberts, Lezah

Serial No.: 10/728,277

) RULE 132 DECLARATION

Filed: December 4, 2003

) OF JANICE M. TROHA

) (37 C.F.R. § 1.132)

Conf. No.: 7142

)

Atty. File No.: 42830-10010

)

For: "TREATMENT OF MUCOSITIS"

)

Assistant Commissioner for Patents
Washington, D.C. 20231

| | |
|--|----------------------------------|
| CERTIFICATE OF MAILING | |
| I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, DC 20231 ON <u>9-25-06</u> . | |
| BY: | MARSH, FISCHMAN & BREYFOGLE, LLP |
|  | |

I, Janice M. Troha, residing at 7394 Cortez Lane, Boulder, CO 80303, declare as follows:

Qualifications And Basis For Declaration:

I am currently employed in the capacity of Vice President, Clinical Development Regulatory Affairs at RxKinetix, Inc. ("RxKinetix"), the assignee of referenced U.S. Patent Application No. 10/728,277 (the "Pending Application"). In my current position, I have worked extensively, and gained considerable experience in the area of oral mucositis as a side effect of cancer therapy.

The attached Exhibit A is a summary of my technical qualifications.

The attached Exhibit B includes tabular data from an animal study in hamsters concerning the use of N-acetylcysteine ("NAC") for the treatment of radiation-induced oral mucositis.

I have reviewed and considered the Pending Application, including pending claims, and an Office Action dated March 23, 2006 issued by the United States Patent and Trademark Office on March 23, 2006 (the "Office Action") concerning the Pending Application.

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I have reviewed and considered U.S. Patent Number 5,358,705 by Boggs et al. ("Boggs et al.") and U.S. Patent Number 6,503,955 by Dobrozsi et al. ("Dobrozsi et al."), which have been cited by the patent Examiner in the Office Action.

Mucositis:

Oral mucositis has long been recognized as a common and often debilitating side effect of cancer therapy. In patients with head and neck cancer who receive high doses of radiation as part of their cancer treatment the incidence of severe mucositis is high. Furthermore, there is no treatment for oral mucositis that is currently approved by the United States Food and Drug Administration for use in these patients. Oral mucositis begins in the endothelial layer of the oral mucosa, or endothelium. The oral mucosa is comprised of three distinct layers, the first being the epithelial layer or outer surface of the mucosa, the second layer is the lamina propria and the third and deepest layer of the oral mucosa is the endothelium, also referred to as the submucosa. Chemotherapy and radiotherapy initiate inflammatory changes that begin in the endothelial layer of the oral mucosa. These changes then set up a cascade of events that extend to the epithelium and the surface of the oral cavity tissues. At first these changes appear as reddened inflamed tissue and, eventually, as ulcers. These ulcers may be superficial or deep and necrotic depending on the severity of the disease. Bacteria are not involved in the initial stages of oral mucositis. The presence of bacteria in the oral cavity may complicate the progression of mucositis and the healing process, once ulcers have developed, but they are not a causative factor. Antibacterial agents have been tested in patients with oral mucositis, but I am not aware of any antibacterial agent that has been found to be effective for treating oral mucositis, further refuting any role for bacteria as a causative factor in the pathogenesis of oral mucositis. Development of mucositis at other locations in the body as a side effect of cancer therapy would be mechanistically similar to that described above for oral mucositis. The discussion here focuses on oral mucositis, but the same general principles apply to mucositis occurring at other locations.

The World Health Organization ("WHO") and the National Cancer Institute ("NCI") have each developed scales for assessing the severity of oral mucositis resulting from cancer therapy, with a greater score on each scale indicating a more severe form of oral mucositis. Although a desirable treatment for oral mucositis would result in lower overall oral mucositis

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scores by patients, it is particularly desirable that the treatment reduces the number of patients developing severe oral mucositis. Severe oral mucositis is indicated by a score of 3 or greater on the WHO or NCI oral mucositis toxicity scales. The progression from a score of 2 to a score of 3 is highly clinically significant, even though there is only one incremental point difference between the scores.

A score of 2 on the WHO or NCI scales represents moderate oral mucositis. Patients developing such moderate oral mucositis may require aggressive pain management but they are able to maintain adequate oral intake and do not normally require aggressive clinical interventions, such as feeding tubes, cessation of cancer treatment and/or hospitalization. As noted above, a score of 3 or greater is considered severe oral mucositis. Severe oral mucositis often develops in cancer therapy patients undergoing radiation therapy and/or chemotherapy, and development of such severe oral mucositis causes significant morbidity, which can seriously complicate continuance of the cancer therapy. Consequences of developing severe oral mucositis may include prescription of opiate analgesia for pain management, insertion of an external feeding tube for maintenance of adequate nutrition, hospitalization to manage symptoms, and systemic infection. Other consequences of developing severe mucositis may include reduction in doses of chemotherapeutic agents or radiation and delays or even complete discontinuation of radiation therapy or chemotherapy. Such alteration of the cancer treatment regimen adversely impacts curability. The possibility for successful completion of cancer therapy is significantly negatively impacted by the occurrence of severe oral mucositis and there has been and continues to be a significant need for oral mucositis treatments, and especially for a treatment that reduces the incidence of severe oral mucositis in cancer therapy patients.

Dobrozs et al. and Boggs et al. References:

Dobrozs et al. describe their invention as directed to pourable liquid vehicles used to deliver compositions, materials and substances to moistened surfaces and aqueous environments (column 3, lines 2-4). The pourable liquid vehicle is such that as the vehicle acquires moisture during use, the vehicle transforms from a liquid to a gel-like form (column 1, lines 14-16; column 3, lines 36-47; column 4, lines 33-48). Dobrozs et al. provide a long listing of possible substances that could be delivered using the pourable liquid vehicle (column 7, line 26 through column 9, line 27), and as one possibility mention "Expectorants/Mucolytics" including, among

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other things, NAC. Expectorants and mucolytics are agents used to breakdown and expel mucous from the respiratory tract. The disclosed possible use of NAC as an expectorant or mucolytic is not indicative of efficacy for the treatment of oral mucositis, and the disclosure of Dobrozszi et al. would not lead to an expectation, nor predict that NAC has efficacy for the treatment of oral mucositis. The demonstration of efficacy as an expectorant or mucolytic, to remove material from the surface of the mucosal membrane is entirely unrelated to the condition of oral mucositis and would not be indicative of efficacy to treat a condition such as oral mucositis, which develops beginning in the endothelial layer of the oral mucosa, as discussed above.

Boggs et al. describe their invention as being directed to compositions for reducing or preventing dental plaque, or gingival or periodontal diseases, of the oral cavity in humans or lower animals (column 1, lines 44-51). According to Boggs et al., toxins in plaque and calculus (a hard crusty deposit on teeth that can develop from plaque) can irritate the gingival tissues surrounding teeth coated with the plaque or calculus, causing inflammation and destruction of the gums (column 1, lines 29-39). The compositions of Boggs et al. include as an active ingredient a complex of certain metal ions with N-acetylated amino acids (column 1, lines 44-58). Boggs et al. list NAC as being one possibility for the N-acetylated amino acid for use in the active ingredient complex (column 2, line 65 through column 3, line 2). Boggs et al. note that mechanistically, the use of the active ingredient complex leads to a dramatic reduction in bacteria binding to the tooth surface, and because bacteria are impeded from adhering to the teeth, fewer bacteria are present on the tooth surface to multiply, with the result that there is a reduction in the bacterial accumulation, and consequently a reduction in plaque and gingivitis (column 3, lines 34-40 and 54-58).

The disclosure by Boggs et al. would not lead to an expectation, nor predict that NAC has efficacy for the treatment of oral mucositis. The mechanism for action described by Boggs et al. concerning reductions in bacterial binding to the tooth is not indicative of efficacy in relation to the treatment of oral mucositis, the pathogenesis of which does not appear to be due to the presence of bacteria. Moreover, as discussed above, oral mucositis begins in the endothelial layer of the oral mucosa, and not at the superficial level of the surface of the gum or tooth, which is the area of interest to Boggs et al.

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Animal Study On Use Of NAC To Treat Oral Mucositis:

The EXAMPLE presented on pages 24-27 of the Pending Application discusses an animal study conducted in hamsters concerning the use of NAC as an active agent to treat oral mucositis resulting from irradiation. In the study (the details of which are discussed more fully in the Pending Application), oral mucositis was induced in hamsters through targeted irradiation of the left buccal pouch with a total of 40 Gy of radiation on day 0. For 28 days post-irradiation, the hamsters were dosed topically in the oral cavity 3 times per day with either a treatment formulation containing NAC or a control formulation not containing NAC. Compositions of treatment and control formulations are shown in Table 1 of the Pending Application, and the compositions of the control formulations and two selected treatment formulations are repeated in Table D-1 below, for convenience in relation to the discussion provided below.

Table D-1. Compositions Of Selected Test Formulations Used In Animal Study

| Formulation | NAC (Wt %) | Poloxamer 407 ¹ (Wt %) | Chitosan (Wt %) | NaOH (M) | pH |
|--------------------------------------|---------------|--------------------------------------|--------------------|-------------|-----|
| N-acetylcysteine Formulations | | | | | |
| A2.02 | 10 | 16.25 | 0 | 0.57 | 4-5 |
| A2.03 | 10 | 0 | 0 | 0.57 | 5-6 |
| CONTROL FORMULATIONS | | | | | |
| Vehicle control | 0 | 16.25 | 0.5 | 0 | 5-6 |
| Water control | 0 | 0 | 0 | 0 | |

Pluronic® F-127

Beginning on day 6 post-irradiation and continuing every second day thereafter through day 28, mucositis was preliminarily scored by an investigator upon examining the buccal pouch and using a validated photographic scale ranging from 0 for normal to 5 for maximum ulceration. A score of 3 or greater is considered to correspond with development of severe oral mucositis. The results of this preliminary scoring in terms of average mucositis score are shown graphically in Figure 1 of the Pending Application, which is not repeated here. A description of the scoring used in the hamster study is presented in Table 2 of the Pending Application. This scoring scale was developed for use in animal studies to approximate the severity of oral mucositis that would be indicated by the corresponding score on the NCI or WHO scales for

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human patients. Table D-2 below provides a comparison between the oral mucositis scoring scale used in the animal study and the NCI oral mucositis scale.

Table D-2. Oral Mucositis Toxicity Scales Comparison

| Score | Mucositis Toxicity Scale Used in Animal Study | NCI Toxicity Scale Used in Patients |
|-------|---|--|
| 0 | No mucositis | No mucositis |
| 1 | Light to severe erythema and vasodilation. No erosion of the mucosa | Erythema of the mucosa (of any severity) |
| 2 | Severe erythema and vasodilation. Erosion of superficial aspects of mucosa leaving denuded areas. Decreased stippling of mucosa. | Patchy ulcerations or pseudomembranes (patches generally \leq 1.5 cm in diameter and non-contiguous) |
| 3 | Formation of off-white ulcers in one or more places. Ulcers may be yellow/gray due to pseudomembrane. Cumulative size of ulcers should equal about 25% of the pouch ¹ . Severe erythema and vasodilation | Confluent ulcerations or pseudomembranes (contiguous patches generally $>$ 1.5 cm in diameter) |
| 4 | Cumulative size of ulcers should equal about 50% of the pouch. Loss of pliability (pouch can only be partially extracted from the mouth). | Tissue necrosis; significant spontaneous bleeding; life-threatening consequences. |
| 5 | Virtually all of the pouch is ulcerated. Loss of pliability (pouch can only partially be extracted from the mouth) | Death |

¹Refers to hamster cheek pouch

In addition to the preliminary scoring, beginning on day 6 post-irradiation and continuing every second day thereafter, photographs were taken of the buccal pouch of the hamsters. The photographs were subsequently reviewed in blinded fashion by two investigators who each scored oral mucositis as revealed by the photographs, using the same photograph validated scale developed for animal studies, as noted above and summarized in Table D-2. The preliminary scoring provided a good real time indication of mucositis development in the hamsters during the study, but the blinded photographic scoring is considered to be better controlled and more verifiable than the preliminary scoring. Exhibit B contains a tabulation of oral mucositis scores assigned by the investigators in the blind photograph scoring of hamster groups for each of the test formulations shown in Table D-1 above.

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In the blinded scoring, if an animal receives a score of 3 or greater from either investigator on any given day, then that animal is considered to have severe oral mucositis on that day. Table D-3 below summarizes the number and percentage of scoring days for all animals (referred to as animal-days) in each treatment group on which a score of 3 or greater was assigned by either investigator, indicating severe mucositis.

Table D-3. Animal-Days Scored With Severe Mucositis

| | Water Control | Vehicle Control | RK-0203 | RK-0202 |
|--|---------------|-----------------|---------|---------|
| Total Number Animal-Days | 84 | 84 | 72 | 72 |
| Number Animal-Days With Severe Mucositis Score | 51 | 36 | 15 | 3 |
| % Animal-Days With Severe Mucositis Score | 61% | 43% | 21% | 4% |

For the RK-0203 formulation (NAC in water), the lower prevalence of severe mucositis scores (only 21%) is very significant in comparison to the water control formulation (61%), indicating that NAC has significant efficacy in the treatment of oral mucositis. This would not be expected based on the quite different uses for NAC described in the Dobrozsi et al. and Boggs et al. references cited in the Office Action, as discussed above. The results shown in Table D-3 for RK-0202 are particularly striking, with only 4% of the scored animal-days showing severe mucositis scores. Even if NAC had been previously known as being effective for treatment of oral mucositis, this result is very significant and would not be expected based solely on the change in delivery formulation between RK-0203 (NAC in water) and RK-0202 (reverse-thermal gelling composition with poloxamer 407).

It is noted that, as shown in Table D-3, the vehicle control formulation (poloxamer 407, chitosan and water, with no NAC) had a lower incidence of severe mucositis on scored days than the water control formulation (no poloxamer 407 or NAC). Although this result for the vehicle control formulation is interesting, on closer examination of the data presented in Exhibit B it is of only limited, if any, significance in a clinical context concerning treatment for oral mucositis in human patients undergoing cancer therapy.

When human patients undergoing cancer therapy develop severe oral mucositis, it is a development that is detrimental to continuation of the cancer therapy, and calls for immediate attention. The cancer therapy will typically involve multiple radiation and/or chemotherapeutic doses given at periodic intervals. The human patient does not have the benefit of a significant

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recovery period between doses, and the next cancer treatment dose is an aggravating event for oral mucositis that has already developed. From a clinical perspective, considering human patients undergoing cancer therapy, the number of animals in each study group that developed severe mucositis at some time during the animal study is highly relevant, whether or not oral mucositis scores thereafter decreased during the animal study.

Table D-4 summarizes data from Exhibit B concerning the incidence, by test group, of animals receiving an oral mucositis score indicative of severe oral mucositis at some time during the animal study. An animal is considered to have developed severe oral mucositis if the animal reached a score of 3 or greater from either investigator on any day scored during the study.

As seen in Table D-4, by day 16 all of the animals in the water control and vehicle control groups had reached a severe oral mucositis score. For RK-0203, 5/6 or 83% of the animals reached a severe oral mucositis score, and attainment of that level occurred on day 18. Strikingly, only 2/6 or 33% of the animals in the RK-0202 group reached a severe oral mucositis score. Also significant for RK-0202 is that no animal in that group received a severe mucositis score until day 14, later than any of the other groups. This apparent delay in the onset of severe mucositis and lower overall number of animals reaching a severe mucositis score for the RK-0202 group is very significant and surprising, and especially so in comparison to the RK-0203 group, which received the same amount of the NAC active ingredient. The significant reduction in the total number of animals receiving a severe oral mucositis score using RK-0202 compared to RK-0203 would not be expected due simply to the change in the delivery vehicle (reverse-thermal gelling composition with poloxamer 407 vs. water).

Table D-4. Animals Developing Severe Mucositis During Study

| | Water Control | Vehicle Control | RK-0203 | RK-0202 |
|---|---------------|-----------------|---------|---------|
| Fraction Animals That Developed Severe Mucositis | | | | |
| Through Day 6 | 0/7 | 0/7 | 0/6 | 0/6 |
| Through Day 8 | 0/7 | 0/7 | 1/6 | 0/6 |
| Through Day 10 | 1/7 | 0/7 | 1/6 | 0/6 |
| Through Day 12 | 4/7 | 2/7 | 3/6 | 0/6 |
| Through Day 14 | 5/7 | 6/7 | 3/6 | 1/6 |
| Through Day 16 | 7/7 | 7/7 | 4/6 | 1/6 |
| Through Day 18 | 7/7 | 7/7 | 5/6 | 1/6 |
| Through Day 20 | 7/7 | 7/7 | 5/6 | 2/6 |
| Through Day 22 | 7/7 | 7/7 | 5/6 | 2/6 |
| Through Day 24 | 7/7 | 7/7 | 5/6 | 2/6 |
| Through Day 26 | 7/7 | 7/7 | 5/6 | 2/6 |
| Through Day 28 | 7/7 | 7/7 | 5/6 | 2/6 |
| % Animals That Developed Severe Mucositis | | | | |
| Through Day 6 | 0% | 0% | 0% | 0% |
| Through Day 8 | 0% | 0% | 17% | 0% |
| Through Day 10 | 14% | 0% | 17% | 0% |
| Through Day 12 | 57% | 29% | 50% | 0% |
| Through Day 14 | 71% | 86% | 50% | 17% |
| Through Day 16 | 100% | 100% | 67% | 17% |
| Through Day 18 | 100% | 100% | 83% | 17% |
| Through Day 20 | 100% | 100% | 83% | 33% |
| Through Day 22 | 100% | 100% | 83% | 33% |
| Through Day 24 | 100% | 100% | 83% | 33% |
| Through Day 26 | 100% | 100% | 83% | 33% |
| Through Day 28 | 100% | 100% | 83% | 33% |

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Phase 2 Clinical Trial:

A phase 2, prospective, randomized, placebo-controlled, double-blind study was conducted to compare the effect of two treatment formulations (Formulation 1 containing 5% NAC and Formulation 2 containing 10% NAC) with placebo on the incidence of severe oral mucositis in human patients treated with radiation therapy (RT) for head and neck cancer. Each of the treatment formulations contained sufficient poloxamer 407 (Pluronic® F-127) to impart reverse-thermal gelation properties to the test formulations. The compositions of the test formulations are summarized in Table D-5 below.

Table D-5 Compositions of Treatment Formulations

| Component | Formulation 1 | Formulation 2 |
|----------------------------|---------------------|----------------------|
| | (5% NAC) % (w/w) | (10% NAC) % (w/w) |
| NAC | 5.00 | 10.00 |
| Poloxamer 407 ¹ | 13.00 | 13.00 |
| Calcium Sodium EDTA | 0.09 | 0.09 |
| Methyl Paraben | 0.20 | 0.20 |
| Sodium Citrate | 0.29 | 0.29 |
| Sodium Hydroxide | 1.225 | 2.450 |
| Sterile Water | 77.70 | 71.50 |
| Sucralose | 0.050 | 0.050 |
| Pure Lemon Extract | 2.40 | 2.40 |

¹ Pluronic® F-127 or Lutrol® F-127

The study was conducted at 15 sites in North America (12 in the US; 3 in Canada). The protocol was approved by the institutional or ethics review board at each site. All patients gave written informed consent before entry and before study related procedures were performed. Eligible patients had confirmed cancers of the oral cavity, oropharynx, nasopharynx or salivary glands; were at least 18 years of age; had a Karnofsky performance status of at least 60 and were scheduled to receive at least 60 Gy of RT. The planned volume had to include at least 3 oral qualifying sites, defined as one that would receive at least 60 Gy to 2 cm². RT could consist of 1.8 to 2.2 Gy per day in single fractions and up to 3.3 Gy during concurrent boost. Patients were excluded from the study if they were to receive concomitant chemotherapy, amifostine or pilocarpine, or if they had evidence of oral mucositis at baseline, prior RT to the head and neck, or hypopharyngeal tumors. Patients with a medical or sociological, or psychological impairment

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that would likely affect their compliance with the protocol were also excluded. Concomitant use of oral antifungals, topical and systemic analgesics as well as palliative mouth rinses consisting of viscous lidocaine, milk of magnesia, baking soda and salt were allowed. A standard, oral care protocol was followed at each institution. Patients were instructed to brush their teeth twice daily, floss once daily, apply fluoride treatments and refrain from wearing dentures. Commercial mouthwashes were prohibited. Patients rinsed with the treatment formulation or placebo 6 times daily during their RT. The 5% NAC dosage strength treatment formulation (Formulation 1) was eliminated at interim analysis by an Independent Data Monitoring Committee due to a lower effect compared with the 10% NAC dosage strength treatment formulation (Formulation 2). The primary comparison was, therefore, between Formulation 2 and placebo in the intent-to-treat population. Analyses of all efficacy and safety endpoints included all qualifying patients who underwent randomization and received at least one dose of study drug. The efficacy of the treatment formulations was assessed by evaluating the incidence of grade ≥ 3 oral mucositis, by a cumulative dose of 60 Gy of radiation, using both the WHO and NCI toxicity scales. The data was analyzed using a time-to-failure approach, with cumulative RT dose substituted for time, and the interval specified as 0 to 60 Gy. Patients with WHO or NCI grade 0, 1, or 2 oral mucositis were defined as successes and those with a grade ≥ 3 as failures. Any patient that reached a WHO or NCI score of 3 was carried forward as a failure throughout RT regardless of whether they subsequently discontinued treatment or returned to a lower score. Efficacy was also assessed by evaluating the need for opiate analgesia and surgically placed feeding tubes. Table D-6 summarizes the WHO and NCI oral mucositis toxicity scales that were used.

Table D-6. WHO and NCI Oral Mucositis Toxicity Scales

| Score | Description | |
|-------|---|---|
| | WHO Toxicity Scale | NCI Toxicity Scale |
| 0 | None | None |
| 1 | Soreness and erythema | Erythema of the mucosa (of any severity) |
| 2 | Erythema, ulcers, maintains ability to eat solids | Patchy ulcerations or pseudomembranes (patches generally ≤ 1.5 cm in diameter and non-contiguous) |
| 3 | Ulcers, requires liquid diet | Confluent ulcerations or pseudomembranes (contiguous patches generally > 1.5 cm in diameter) |
| 4 | Ulceration present, alimentation not possible | Tissue necrosis; significant spontaneous bleeding; life-threatening consequences. |
| 5 | NA | Death |

As shown in the table below, the baseline demographic and disease characteristics of the patients were generally similar among the groups (Table D-7). Compliance was good with a mean number of daily doses of 5.1 out of 6, and 80% of patients rating the study drug as acceptable.

Table D-7. Baseline Patient Characteristics

| Group Number | Formulation 2 38 | Placebo 29 |
|--|---------------------|---------------|
| Age-mean (sd) | 58 (14) | 59 (14) |
| Median | 56 | 58 |
| Gender -- % males | 61% | 69% |
| Smoking Pack Years – Mean (sd) | 24.2 (21.4) | 31.8 (38.7) |
| Median | 16.8 | 20 |
| Current Smokers – Number (%) | 4 (11%) | 4 (14%) |
| Drinks Per Day – Mean (sd) | 2.6 (2.71) | 1.7 (2.01) |
| Median | 1.5 | 1 |
| Current Drinkers – Number (%) | 17 (45%) | 11 (38%) |
| Planned RT in Gy | | |
| Total Dose – Mean (sd) | 64.2 (4.9) | 64.2 (4.5) |
| Mean | 63 | 66 |
| Daily Dose – Mean (sd) | 1.97 (0.13) | 2.04 (0.15) |
| Median | 2.00 | 2.00 |
| Concurrent Boost Number (%) | 13 (34%) | 10 (34%) |
| Qualifying Oral Cavity Sites Mean (sd) | 6 (3) | 6 (3) |
| Median | 5 | 5 |

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The incidence of WHO grade ≥ 3 oral mucositis by 50 Gy in the Formulation 2 group was 29% lower than in the placebo group ($p = 0.041$; log-rank test) [Table D-8]. The relative reduction in WHO grade ≥ 3 oral mucositis on Formulation 2 at 50 Gy, compared with placebo, was 54%. Formulation 2 also reduced NCI clinical grade ≥ 3 oral mucositis with an absolute reduction in incidence of 46% at 50 Gy compared with placebo ($p = 0.005$; Log-rank test) and a relative reduction of 52%. The incidence of surgically placed PEG tubes for oral mucositis was also significantly lower on Formulation 2 compared with placebo (3% vs. 21%, $p = 0.037$; Fisher's exact test). [Table D-9] Opiate use was also lower in patients receiving Formulation 2 compared with placebo. The median total opiate score was 6 vs. 27, $p = 0.09$, and the median % of days on opiates during the study was 6% vs. 21%. ($p = 0.09$; Wilcoxon rank sum test)

Table D-8. Percentage of Patients Reaching Grade 3 or Greater on the WHO and NCI Scales

| Cumulative dose of radiation in Gy | WHO Toxicity Scale | | NCI Toxicity Scale | |
|------------------------------------|--------------------|---------|--------------------|---------|
| | Formulation 2 | Placebo | Formulation 2 | Placebo |
| 40 Gy | 24% | 46% | 39% | 67% |
| 50 Gy | 25% | 54% | 42% | 88% |
| 60 Gy | 35% | 54% | 63% | 92% |

Table D-9. Incidence of Interventional PEG Tube Placement¹

| | Placebo | Formula 2 |
|--|---------|-----------------|
| | 22% | 3% ² |

¹ Patients with pre-existing PEG tubes excluded

² $p=0.037$; Fisher's exact test

The large reductions in the incidence of severe oral mucositis, WHO or NCI score greater than or equal to 3, in patients treated with Formula 2 relative to placebo is significant, and further confirms significant efficacy of NAC formulated with poloxamer 407 in a reverse-thermal gelling composition for use to treat oral mucositis resulting from cancer therapy. As previously discussed, patients with WHO or NCI grade 0, 1, or 2 oral mucositis were defined as

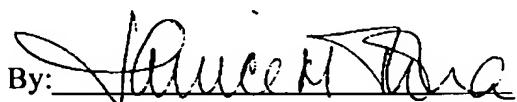
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successes and those with a grade ≥ 3 as failures. The reason for the dichotomization is due to the recognition that a score of 3 represents a highly morbid clinical event. Clinicians and regulatory agencies also recognize the importance of this dichotomization and the clinical impact to patients if they can be prevented from progressing to this point. The FDA has designated the Formula 2-type composition in oral mucositis as qualifying for Fast Track status because it is being investigated for the reduction of severe oral mucositis.

All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true. I understand that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. §1001) and may jeopardize the validity of this patent application or any patent issuing thereon.

Respectfully submitted,

Date: Sept 25th, 2006

By: 

Janice M. Troha

Exhibit A
To Declaration of Janice M. Troha

Curriculum Vitae
Janice M. Troha

Professional Experience

Aug 2001-
Present **RxKinetix, Inc.**
 Boulder, Colorado

Vice President, Clinical Development and Regulatory Affairs
Treasurer, Secretary and Member of the Board of Directors (since 2004)

This position includes specific responsibilities for product development as well as considerable responsibility for general oversight of the company, including its strategic direction and operational performance. Key accomplishments include:

Conversion of the Company's business paradigm from a drug delivery focus to one that is focused on product development in the oncology care arena.

Redirection of the development strategy for the Company's lead product in oral mucositis and successful completion of Phase 2 development, thereby significantly increasing the valuation of the Company for shareholders.

Identification of product opportunities for the RxKinetix pipeline and creation of development strategies for such compounds to further enhance shareholder return.

Establishment and maintenance of relationships with experts to enhance visibility and development programs for RxKinetix products.

1994 - 1999 **Cortech, Inc.**
 Denver, Colorado

1998 - 1999 **Vice President, Product Development**

Responsible for the development of Cortech's technology portfolio, seeking collaborative/merger partners to further such development, and managing existing corporate collaborations and corporate communications. Key accomplishments in this position included:

Securement of a corporate partner for Cortech's lead neutrophil elastase inhibitor program.

Prevention of delisting from the Nasdaq through successful representation of the Company and its business to the Nasdaq listing panel.

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Transition of the Company's business through an acquisition

1996 - 1998 **Senior Director, Clinical Development and Regulatory Affairs**
(reporting directly to the CEO)

Responsible for product and business development, regulatory affairs and corporate communications. Product development responsibilities included leadership of Cortech's stroke program (in preclinical development). Business development responsibilities included seeking collaborative partnerships for Cortech's protease inhibitor technology and the company's lead elastase and bradykinin antagonists. Communications responsibilities included preparation of press releases and sections of annual and quarterly reports that described Cortech's business. Regularly participated in shareholder meetings and conference calls regarding earnings. As a member of the management team, key accomplishments during this period were:

Modification of the company's business paradigm

Significant restructuring of operations and workforce.

1994 - 1996 **Director, Clinical Development**

Responsible for directing the clinical staff (approximately 17) in the clinical development of investigational compounds in the areas of traumatic brain injury, multiple trauma, cystic fibrosis, ARDS and sepsis. Accomplishments in this position included:

Successful conduct of one EOP2 meeting and two pre-IND meetings

Successful completion of Phase 2 clinical development for a product in acute traumatic brain injury. This resulted in a partnership with a large multinational pharma partner.

Preparation of an integrated safety summary that supported lifting the clinical hold on one of Cortech's compounds.

IND filing for the first human neutrophil elastase inhibitor to be studied in man, and initiation of clinical development.
(Phase Ib).

1984 - 1994 **Boehringer Ingelheim Pharmaceuticals, Inc.**
Ridgefield, Connecticut

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1993 - 1994 Associate Director, International Medical Operations

Responsible for overseeing the operations of the U.S. Medical Department and the integration and optimization of Medical Department processes and procedures worldwide. Reported directly to the U.S. Medical Director and participated in executive meetings. Key accomplishments included:

Re-engineering and consolidation of Medical Department structure and processes worldwide. The latter accomplished through appointment to an international team of 15 senior delegates led by the Boston Consulting Group.

Revision of all Medical Department job descriptions to create technical and managerial career tracks.

Preparation of international and national Medical Department SOPs.

1989 - 1993 Associate Director, Clinical Research

First non-MD in the company to achieve this position. Responsible for compound development from Phase I to Phase IV with five direct reports. Also responsible for the creation of an international training program on GCPs through leadership of the Company's International Training Committee. Specific accomplishments included the following:

International Medical Project Leader for an investigational compound in congestive heart failure. Successfully directed the program from IND filing through Phase III clinical development. Responsible for end-of-Phase II meeting with FDA. Designed and set up a large mortality trial.

Medical Project Leader for the development of a monoclonal antibody (Anti-ICAM) in cardiac transplantation and restenosis. Prepared medical sections of the IND and Phase Ib protocol in patients undergoing cardiac transplant.

Phase IV responsibility for antiarrhythmic and antihypertensive agents, including development and oversight of Phase IV trials and review of promotional materials.

Creation and conduct of a worldwide training program on Good Clinical Practices and clinical drug development for Medical Department personnel.

1987 - 1989 Manager, Clinical Research

Responsible for overseeing the implementation, conduct and reporting of clinical trials with two direct reports.

1984 - 1987 Medical Research Associate, Clinical Research

Assisted in the set up, monitoring, and analysis of Phase I-III trials and NDA preparation for an antiarrhythmic agent.

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1982 - 1984 **Clinical Research Center, Tulane Medical Center,
headed by Professor G. McMahon**

Study Coordinator

Responsible for the conduct of Phase II and III clinical trials in cardiovascular indications.

1981 - 1982 **St. Charles General Hospital**
New Orleans, Louisiana

Staff Nurse on a unit which functioned as a step down from ICU.

Education

British education evaluated by the International Education Research Foundation (IERF) and rated as the equivalent of a Master's degree level in the USA.

1984 State University of New York
BS in Liberal Arts and Sciences

1980 Nightingale School of Westminster Hospital
London, England
Honors degree course in nursing - completed three years of course work for licensure.

Areas of specialization included neonatal intensive care, open heart surgery and bone marrow transplantation.

1976 University of Sheffield – Completed first year honors degree course in Pure Mathematics and Statistics then transferred to The Nightingale School.
Member of the University Officers Training Corps.

Publications

Katz S, Wahl J, Troha J, Sonnenblick E, and LeJemtel T. Specific Phosphodiesterase Inhibition and Maximal and Submaximal Exercise performance in Patients with Congestive Heart Failure. *J. Cardiovasc Pharmacol* 1989; 14 (Suppl 2): S45 - S48.

Katz S, Kubo S, Jessup M, Brozena S, Troha J, Wahl J, Cohn J, Sonnenblick E, and LeJemtel T. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Pimobendan, a New Cardiotonic and Vasodilator Agent, in Patients with Severe Congestive Heart Failure. *AHJ* 1992; 123:95-103.

Kubo S, Gollub S, Bourge R, Rahko P, Cobb F, Jessup M, Brozena S, Brodsky M, Kirlin P, Shanes J, Konstam M, Gradman A, Morledge J, Cinquegrani M, Singh S, LeJemtel T, Nicklas J, Troha J, and Cohn J. For the Pimobendan Multicenter Research Group. Beneficial Effects of Pimobendan on Exercise Tolerance and Quality of Life in Patients with Heart Failure: Results of a Multicenter Trial. *Circulation* 1992; 85:942-949.

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Narotam P.K., Rodell T.C., Troha J.M., Bhoola K.D., and van Dellen J.R. Traumatic Brain Contusions: A Clinical Role for the Kinin Antagonist CP-0127. *Acta Neurochirurgica* 1998; 140: 793 - 803.

Marmarou A, Nichols J, Burgess J, Newell D, Troha J, Burnham D, Pitts L and the American Brain Injury Consortium Study Group. Effects of the Bradykinin Antagonist Bradycor™ (Deltibant, CP-0127) in Severe Traumatic Brain Injury: Results of a Multicenter, Randomized, Placebo-controlled Trial. *J. Neurotrauma* 1999; 16: 431 -444

Abstracts

Chambers M.S., Welsh D.V., Scrimger R.A., Zhen W., Epstein J.B., Troha J.M., and Sonis S.T. RK-0202 for Radiation Induced Oral Mucositis. *Journal of Clinical Oncology, 2006 ASCO Annual Meetings Proceedings Part I. Vol 24, No 18S, 2006: 5523.*

Troha J.M., and Rodell, T.C. Experience with the experimental bradykinin antagonist Bradycor™ (CP-0127) in patients with the systemic inflammatory response syndrome (SIRS) and sepsis. Results of two clinical trials. Kinin '95 Fourteenth International Symposium on Kinins, September 10-15, 1995, Denver, CO. Immunopharmacology, 1996.

Shanies H.M., Kaufman L., Fletcher E.C., Westerman J., Matuschak G.M., Taylor Jr. R., Fein A.M., Levy H., Multz A., Rumbak M., Foulke G.E., Seneff M., Oakley R.D., Knaus W.A., Troha J.M., Sandhaus R.A., Rodell T.C.: CP-0127 (BradyCor™), a bradykinin antagonist, in SIRS and sepsis: results from the second multi-center trial using a seven-day infusion. *Chest*, 108:3, 1995.

Chambers M.S., Welsh D.V., Scrimger R.A., Zhen W., Epstein J.B., Sonis S.T.: RK-0202 for Radiation-Induced Oral Mucositis. ASCO, June 2006.

Industry- Related Documents

Authored the following documents:

Medical sections of three INDs and six Investigator Brochures, more than ten clinical trial protocols, six clinical trial reports, two integrated summaries of safety and one integrated summary of efficacy.

Invited Presentations

Results of a multi-center, randomized, placebo-controlled trial of CP-0127, a novel bradykinin antagonist, in patients with SIRS and sepsis. IBC's Fifth Annual Conference on Endotoxemia and Sepsis, June 19-21, 1995, Philadelphia, PA.

Troha J.M., and Rodell, T.C. Experience with the experimental bradykinin antagonist Bradycor™ (CP-0127) in patients with the systemic inflammatory response syndrome (SIRS) and sepsis. Results of two clinical trials. Kinin '95 Fourteenth International Symposium on Kinins, September 10-15, 1995, Denver, CO.

International Data. PERI's Annual Data Management Workshop 1993 to 1997.

CRAs and Data Managers - A Critical Link. PERI's Annual Data Management Workshop 1993 to 1997.

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Exhibit B
To Declaration of Janice M. Troha

Hamster Animal Study
Data From Blinded Photographic Oral Mucositis Scoring

Shown below are the individual oral mucositis scores that were assessed from photographs in a blinded fashion by two investigators in a hamster animal study (2 scores per animal per day of assessment, for a total of 12 – 14 scores per treatment group per day of assessment). Also shown are the means, standard deviation (SD), and standard error of the mean (SEM) of the scores. The initial N=7 hamsters per treatment group was decreased to N=6 in some groups due loss to anesthesia overdose or irradiation which occurred prior to mucositis assessment.

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| Animal | Days post-irradiation | | | | | | | | | | | |
|-----------------|-----------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 |
| Water Control | | | | | | | | | | | | |
| 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| | 2 | 1 | 2 | 4 | 3 | 3 | 4 | 4 | 4 | 3 | 3 | 3 |
| 2 | 1 | 1 | 1 | 3 | 4 | 4 | 4 | 3 | 4 | 4 | 3 | 3 |
| | 1 | 1 | 1 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 3 | 4 |
| 3 | 1 | 0 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 |
| | 1 | 1 | 1 | 2 | 3 | 3 | 4 | 3 | 3 | 3 | 3 | 3 |
| 4 | 1 | 1 | 1 | 2 | 2 | 3 | 1 | 3 | 1 | 1 | 1 | 1 |
| | 1 | 1 | 1 | 2 | 2 | 3 | 1 | 2 | 1 | 2 | 1 | 2 |
| 5 | 1 | 1 | 1 | 0 | 2 | 2 | 2 | 3 | 3 | 3 | 1 | 3 |
| | 1 | 1 | 1 | 1 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 6 | 1 | 2 | 2 | 4 | 4 | 3 | 2 | 3 | 2 | 3 | 3 | 2 |
| | 1 | 1 | 2 | 4 | 4 | 4 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | 1 | 1 | 1 | 3 | 3 | 3 | 2 | 3 | 2 | 1 | 2 | 1 |
| | 0 | 1 | 1 | 3 | 3 | 4 | 3 | 3 | 3 | 2 | 1 | 2 |
| Mean | 1.0 | 1.0 | 1.4 | 2.6 | 3.0 | 3.2 | 2.8 | 3.1 | 2.8 | 2.7 | 2.3 | 2.6 |
| SD | 0.4 | 0.4 | 0.6 | 1.2 | 0.8 | 0.6 | 1.1 | 0.5 | 1.0 | 0.9 | 0.9 | 0.9 |
| SEM | 0.1 | 0.1 | 0.2 | 0.4 | 0.2 | 0.2 | 0.3 | 0.1 | 0.3 | 0.3 | 0.3 | 0.2 |
| Vehicle Control | | | | | | | | | | | | |
| 1 | 0 | 0 | 1 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 1 | 2 |
| | 0 | 0 | 1 | 2 | 3 | 3 | 4 | 3 | 3 | 3 | 2 | 3 |
| 2 | 0 | 1 | 2 | 2 | 3 | 2 | 2 | 2 | 1 | 1 | 1 | 2 |
| | 0 | 1 | 2 | 2 | 3 | 2 | 3 | 3 | 2 | 1 | 2 | 2 |
| 3 | 1 | 0 | 2 | 2 | 3 | 4 | 3 | 3 | 2 | 2 | 2 | 2 |
| | 1 | 0 | 2 | 2 | 3 | 4 | 3 | 3 | 3 | 3 | 3 | 2 |
| 4 | 1 | 1 | 1 | 2 | 3 | 3 | 2 | 2 | 2 | 2 | 2 | 1 |
| | 1 | 1 | 2 | 2 | 3 | 3 | 3 | 3 | 2 | 3 | 2 | 1 |
| 5 | 2 | 1 | 1 | 2 | 2 | 3 | 2 | 2 | 1 | 1 | 1 | 1 |
| | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 2 | 2 | 1 | 1 | 1 |
| 6 | 1 | 2 | 2 | 2 | 3 | 2 | 3 | 2 | 1 | 1 | 2 | 2 |
| | 1 | 1 | 1 | 3 | 3 | 2 | 3 | 3 | 2 | 2 | 2 | 2 |
| 7 | 0 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 3 | 3 | 3 | 2 |
| | 1 | 2 | 2 | 3 | 3 | 2 | 3 | 3 | 3 | 3 | 3 | 2 |
| Mean | 0.8 | 0.9 | 1.6 | 2.1 | 2.8 | 2.7 | 2.8 | 2.6 | 2.2 | 2.0 | 2.0 | 1.8 |
| SD | 0.7 | 0.7 | 0.5 | 0.4 | 0.4 | 0.7 | 0.6 | 0.5 | 0.8 | 0.9 | 0.8 | 0.6 |
| SEM | 0.2 | 0.2 | 0.1 | 0.1 | 0.1 | 0.2 | 0.2 | 0.1 | 0.2 | 0.3 | 0.2 | 0.2 |
| NAC in Water | | | | | | | | | | | | |
| 1 | | | | | | | | | | | | |
| 2 | 1 | 1 | 1 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 2 | 2 |
| | 1 | 1 | 1 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 2 | 2 |
| 3 | 1 | 1 | 1 | 3 | 2 | 2 | 1 | 0 | 2 | 1 | 1 | 2 |
| | 1 | 1 | 1 | 2 | 2 | 2 | 1 | 1 | 2 | 1 | 1 | 2 |
| 4 | 1 | 3 | 2 | 2 | 2 | 2 | 1 | 1 | 2 | 1 | 2 | 2 |
| | 1 | 3 | 2 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 2 |
| 5 | 1 | 1 | 1 | 2 | 2 | 3 | 2 | 2 | 2 | 3 | 3 | 1 |
| | 1 | 1 | 1 | 1 | 2 | 3 | 2 | 3 | 3 | 3 | 3 | 1 |
| 6 | 2 | 1 | 1 | 1 | 2 | 2 | 2 | 1 | 2 | 1 | 1 | 1 |
| | 2 | 1 | 1 | 2 | 2 | 2 | 3 | 2 | 3 | 1 | 1 | 2 |
| 7 | 1 | 1 | 1 | 3 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 2 |
| | 2 | 1 | 2 | 2 | 2 | 2 | 4 | 3 | 4 | 3 | 3 | 2 |
| Mean | 1.3 | 1.4 | 1.2 | 2.0 | 2.0 | 2.2 | 1.8 | 1.6 | 2.3 | 1.9 | 2.0 | 1.7 |
| SD | 0.5 | 0.8 | 0.4 | 0.6 | 0.0 | 0.4 | 1.0 | 1.0 | 0.8 | 0.9 | 0.9 | 0.5 |
| SEM | 0.1 | 0.2 | 0.1 | 0.2 | 0.0 | 0.1 | 0.3 | 0.3 | 0.2 | 0.3 | 0.2 | 0.1 |
| RK0202 | | | | | | | | | | | | |
| 1 | 1 | 1 | 1 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 2 |
| | 1 | 2 | 1 | 2 | 2 | 2 | 1 | 1 | 2 | 1 | 1 | 2 |
| 2 | 0 | 1 | 1 | 1 | 2 | 2 | 2 | 1 | 2 | 1 | 1 | 1 |
| | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 3 | | | | | | | | | | | | |
| 4 | 1 | 1 | 1 | 1 | 2 | 2 | 1 | 1 | 2 | 1 | 1 | 1 |
| | 1 | 1 | 2 | 1 | 2 | 2 | 1 | 2 | 1 | 1 | 1 | 1 |
| 5 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 |
| | 1 | 2 | 2 | 1 | 2 | 2 | 1 | 3 | 2 | 1 | 1 | 1 |
| 6 | 0 | 1 | 1 | 1 | 2 | 2 | 1 | 2 | 2 | 1 | 1 | 1 |
| | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 |
| 7 | 1 | 1 | 1 | 1 | 2 | 2 | 1 | 3 | 2 | 1 | 1 | 1 |
| | 1 | 1 | 1 | 2 | 3 | 2 | 1 | 2 | 2 | 1 | 2 | 1 |
| Mean | 0.8 | 1.3 | 1.3 | 1.3 | 2.1 | 2.0 | 1.3 | 1.8 | 1.7 | 1.1 | 1.2 | 1.3 |
| SD | 0.4 | 0.5 | 0.5 | 0.5 | 0.3 | 0.0 | 0.5 | 0.7 | 0.5 | 0.3 | 0.4 | 0.5 |
| SEM | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.0 | 0.1 | 0.2 | 0.1 | 0.1 | 0.1 | 0.1 |